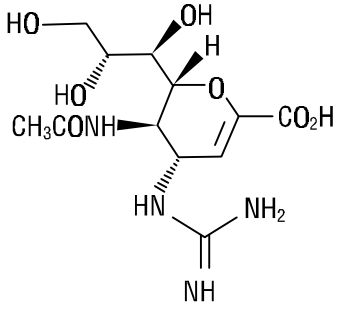
RELENZA®

(zanamivir for inhalation)

For Oral Inhalation Only
For Use with the DISKHALER® Inhalation Device

DESCRIPTION: The active component of RELENZA is zanamivir. The chemical name of zanamivir is 5-(acetylamino)-4-[(aminoiminomethyl)-amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid. It has a molecular formula of $C_{12}H_{20}N_4O_7$ and a molecular weight of 332.3. It has the following structural formula:



Zanamivir is a white to off-white powder with a solubility of approximately 18 mg/mL in water at 20°C.

RELENZA is for administration to the respiratory tract by oral inhalation only. Each RELENZA ROTADISK® contains 4 regularly spaced double-foil blisters with each blister containing a powder mixture of 5 mg of zanamivir and 20 mg of lactose. The contents of each blister are inhaled using a specially designed breath-activated plastic device for inhaling powder called the DISKHALER. After a RELENZA ROTADISK is loaded into the DISKHALER, a blister that contains medication is pierced and the zanamivir is dispersed into the air stream created when the patient inhales through the mouthpiece. The amount of drug delivered to the respiratory tract will depend on patient factors such as inspiratory flow. Under standardized in vitro testing, RELENZA ROTADISK delivers 4 mg of zanamivir from the DISKHALER device when tested at a pressure drop of 3 kPa (corresponding to a flow rate of about 62 to 65 L/min) for 3 seconds. In a study of 5 adult and 5 adolescent patients with obstructive airway diseases, the combined peak inspiratory flow rates ranged from 66 to 140 L/min.

MICROBIOLOGY:

Mechanism of Action: The proposed mechanism of action of zanamivir is via inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.

Antiviral Activity In Vitro: The antiviral activity of zanamivir against laboratory and clinical isolates of influenza virus was determined in cell culture assays. The concentrations of zanamivir required for inhibition of influenza virus were highly variable depending on the assay method used and virus isolate tested. The 50% and 90% inhibitory concentrations (IC_{50} and IC_{90}) of zanamivir were in the range of 0.005 to 16.0 µM and 0.05 to >100 µM, respectively (1 µM = 0.33 µg/mL). The relationship between the in vitro inhibition of influenza virus by zanamivir and the inhibition of influenza virus replication in humans has not been established.

Drug Resistance: Influenza viruses with reduced susceptibility to zanamivir have been recovered in vitro by passage of the virus in the presence of increasing concentrations of the drug. Genetic analysis of these viruses showed that the reduced susceptibility in vitro to zanamivir is associated with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or both.

In an immunocompromised patient infected with influenza B virus, a variant virus emerged after treatment with an investigational nebulized solution of zanamivir for 2 weeks. Analysis of this variant showed a hemagglutinin mutation (Thr 198 Ile) which resulted in a reduced affinity for human cell receptors, and a mutation in the neuraminidase active site (Arg 152 Lys) which reduced the enzyme's activity to zanamivir by 1000-fold.

Insufficient information is available to characterize the risk of emergence of zanamivir resistance in clinical use.

Influenza Vaccine Interaction Study: An interaction study (n = 138) was conducted to evaluate the effects of zanamivir (10 mg once daily) on the serological response to a single dose of trivalent inactivated influenza vaccine, as measured by hemagglutination inhibition titers. There was no clear difference in hemagglutination inhibition antibody titers at 2 weeks and 4 weeks after vaccine administration between zanamivir and placebo recipients.

Influenza Challenge Studies: Antiviral activity of zanamivir was supported for influenza A, and to a more limited extent for influenza B, by Phase I studies in volunteers who received intranasal inoculations of challenge strains of influenza virus, and received an intranasal formulation of zanamivir or placebo starting before or shortly after viral inoculation.

CLINICAL PHARMACOLOGY:

Pharmacokinetics: ***Absorption and Bioavailability:*** Pharmacokinetic studies of orally inhaled zanamivir indicate that approximately 4% to 17% of the inhaled dose is systemically absorbed. The peak serum concentrations ranged from 17 to 142 ng/mL within 1 to 2 hours following a 10-mg dose. The area under the serum concentration versus time curve (AUC_{∞}) ranged from 111 to 1364 ng•h/mL.

Distribution: Zanamivir has limited plasma protein binding (<10%).

Metabolism: Zanamivir is renally excreted as unchanged drug. No metabolites have been detected in humans.

Elimination: The serum half-life of zanamivir following administration by oral inhalation ranges from 2.5 to 5.1 hours. It is excreted unchanged in the urine with excretion of a single dose completed within 24 hours. Total clearance ranges from 2.5 to 10.9 L/h. Unabsorbed drug is excreted in the feces.

Special Populations: Impaired Hepatic Function: The pharmacokinetics of zanamivir have not been studied in patients with impaired hepatic function.

Impaired Renal Function: Systemic exposure is limited after inhalation (see Absorption and Bioavailability). After a single intravenous dose of 4 mg or 2 mg of zanamivir in volunteers with mild/moderate or severe renal impairment, respectively, significant decreases in renal clearance (and hence total clearance: normals 5.3 L/h, mild/moderate 2.7 L/h, and severe 0.8 L/h; median values) and significant increases in half-life (normals 3.1 h, mild/moderate 4.7 h, and severe 18.5 h; median values) and systemic exposure were observed. Safety and efficacy have not been documented in the presence of severe renal insufficiency.

Pediatric Patients: The pharmacokinetics of zanamivir have not been studied in pediatric patients under 12 years of age with influenza (see PRECAUTIONS: Pediatric Use).

Geriatric Patients: The pharmacokinetics of zanamivir have not been studied in patients over 65 years of age (see PRECAUTIONS: Geriatric Use).

Gender, Race, and Weight: In a population pharmacokinetic analysis in patient studies, no clinically significant differences in serum concentrations and/or pharmacokinetic parameters (V/F, CL/F, ka, AUC_{0-3}, C_{max}, T_{max}, CLr, and % excreted in urine) were observed when demographic variables (gender, age, race, and weight) and indices of infection (laboratory evidence of infection, overall symptoms, symptoms of upper respiratory illness, and viral titers) were considered. There were no significant correlations between measures of systemic exposure and safety parameters.

Drug Interactions: No clinically significant pharmacokinetic drug interactions are predicted based on data from in vitro studies.

Zanamivir is not a substrate nor does it affect cytochrome P450 (CYP) isoenzymes (CYP1A1/2, 2A6, 2C9, 2C18, 2D6, 2E1, and 3A4) in human liver microsomes.

INDICATIONS AND USAGE: RELENZA is indicated for treatment of uncomplicated acute illness due to influenza virus in adults and adolescents 12 years and older who have been symptomatic for no more than 2 days. This indication is based on studies in which the predominant influenza infections were influenza A, and a limited number of patients with influenza B were also enrolled (see Description of Clinical Studies and PRECAUTIONS).

Description of Clinical Studies: The efficacy of RELENZA 10 mg inhaled twice daily for 5 days in the treatment of influenza has been evaluated in placebo-controlled studies conducted in North

America, the Southern Hemisphere, and Europe during their respective influenza seasons. The magnitude of treatment effect varied between studies, with possible relationships to population-related factors including amount of symptomatic relief medication used.

Populations Studied: The principal phase 3 studies enrolled 1588 patients ages 12 years and older (median age 34 years, 49% male, 91% Caucasian), with uncomplicated influenza-like illness within 2 days of symptom onset. Influenza was confirmed by culture, hemagglutination inhibition antibodies, or investigational direct tests. Of 1164 patients with confirmed influenza, 89% had influenza A and 11% had influenza B. These studies served as the principal basis for efficacy evaluation, with more limited phase 2 studies providing supporting information where necessary. Following randomization to either zanamivir or placebo (inhaled lactose vehicle), all patients received instruction and supervision by a healthcare professional for the initial dose.

Principal Results: The definition of time to improvement in major symptoms of influenza included no fever and self-assessment of “none” or “mild” for headache, myalgia, cough, and sore throat. A phase 2 and a phase 3 study conducted in North America (total of over 600 influenza-positive patients) suggested up to one day of shortening of median time to this defined improvement in symptoms in patients receiving zanamivir compared to placebo, although statistical significance was not reached in either of these studies. In a study conducted in the Southern Hemisphere (321 influenza-positive patients), a 1.5-day difference in median time to symptom improvement was observed. Additional evidence of efficacy was provided by the European study.

Other Findings:

- There was no consistent difference in treatment effect in patients with influenza A compared to influenza B; however, these trials enrolled smaller numbers of patients with influenza B and thus provided less evidence in support of efficacy in influenza B (see PRECAUTIONS).
- In general, patients with lower temperature (e.g., 38.2°C or less) or investigator-rated as having less severe symptoms at entry derived less benefit from therapy.
- No consistent treatment effect was demonstrated in patients with underlying chronic medical conditions, including respiratory or cardiovascular disease (see PRECAUTIONS).
- No consistent differences in rate of development of complications were observed between treatment groups.
- Some fluctuation of symptoms was observed after the primary study endpoint in both treatment groups.

CONTRAINDICATIONS: RELENZA is contraindicated in patients with a known hypersensitivity to any component of the formulation.

PRECAUTIONS:

General: Patients should be instructed in the use of the delivery system. Instructions should include a demonstration whenever possible. Patients should read and follow carefully the Patient Instructions for Use accompanying the product. Effective and safe use of RELENZA requires proper use of the DISKHALER to inhale the drug.

There is no evidence for efficacy of zanamivir in any illness caused by agents other than influenza virus A and B. Data on treatment of influenza B are limited (see INDICATIONS AND USAGE: Description of Clinical Studies).

No data are available to support safety or efficacy in patients who begin treatment after 48 hours of symptoms.

Safety and efficacy of repeated treatment courses have not been studied.

Patients with Underlying Respiratory Disease: Safety and efficacy have not been demonstrated in patients with underlying chronic pulmonary disease. In particular, this product has not been shown to be effective, and may carry risk, in patients with severe or decompensated chronic obstructive pulmonary disease or asthma. Bronchospasm was documented following administration of zanamivir in 1 of 13 patients with mild or moderate asthma (but without acute influenza-like illness) in a phase 1 study. In interim results from an ongoing treatment study in patients with acute influenza-like illness superimposed on underlying asthma or chronic obstructive pulmonary disease, more patients on zanamivir than on placebo experienced greater than 20% decline in FEV_1 or peak expiratory flow rate. Some patients with underlying respiratory disease may experience bronchospasm and/or decline in lung function when treated with zanamivir. Any patient who develops bronchospasm or decline in lung function should stop the drug. Patients with underlying respiratory disease should be instructed to have a fast-acting inhaled bronchodilator available when treated with zanamivir.

Prevention of Influenza: Use of zanamivir should not affect the evaluation of individuals for annual influenza vaccination in accordance with guidelines of the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices. Safety and efficacy of zanamivir have not been established for prophylactic use of zanamivir to prevent influenza.

Limitations of Populations Studied: Safety and efficacy have not been demonstrated in patients with high-risk underlying medical conditions (see INDICATIONS AND USAGE: Description of Clinical Studies). No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring inpatient management.

Information for Patients: Patients should be instructed in use of the delivery system. Instructions should include a demonstration whenever possible.

For the proper use of RELENZA, the patient should read and follow carefully the accompanying Patient's Instructions for Use.

Patients should be advised to finish the entire 5-day course of treatment even if they start to feel better sooner.

Patients should be advised that the use of RELENZA for treatment of influenza has not been shown to reduce the risk of transmission of influenza to others.

Patients with asthma or chronic obstructive pulmonary disease should be advised of the potential risk of bronchospasm with zanamivir, should have a fast-acting inhaled bronchodilator available, and should stop zanamivir and contact their physician promptly if they experience worsening respiratory symptoms. Patients scheduled to take inhaled bronchodilators at the same time as RELENZA should be advised to use their bronchodilators before taking RELENZA.

Drug Interactions: No clinically significant pharmacokinetic drug interactions are predicted based on data from in vitro studies.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: ***Carcinogenesis****:* In 2-year carcinogenicity studies conducted in rats and mice using a powder formulation administered through inhalation, zanamivir induced no statistically significant increases in tumors over controls. The maximum daily exposures in rats and mice were approximately 23 to 25 and 20 to 22 times, respectively, greater than those in humans at the proposed clinical dose based on AUC comparisons.

Mutagenesis: Zanamivir was not mutagenic in in vitro and in vivo genotoxicity assays which included bacterial mutation assays in *S. typhimurium* and *E.coli*, mammalian mutation assays in mouse lymphoma, chromosomal aberration assays in human peripheral blood lymphocytes, and the in vivo mouse bone marrow micronucleus assay.

Impairment of Fertility: The effects of zanamivir on fertility and general reproductive performance were investigated in male (dosed for 10 weeks prior to mating, and throughout mating, gestation/lactation, and shortly after weaning) and female rats (dosed for 3 weeks prior to mating through day 19 of pregnancy, or day 21 post partum) at IV doses 1, 9, and 90 mg/kg per day. Zanamivir did not impair mating or fertility of male or female rats, and did not affect the sperm of treated male rats. The reproductive performance of the F1 generation born to female rats given zanamivir was not affected. Based on a subchronic study in rats at a 90-mg/kg per day IV dose, AUC values ranged between 142 and 199 mcg•hr/mL (>300 times the human exposure at the proposed clinical dose).

Pregnancy: Pregnancy Category B. Embryo/fetal development studies were conducted in rats (dosed from days 6 to 15 of pregnancy) and rabbits (dosed from days 7 to 19 of pregnancy) using the same IV doses. Pre- and post-natal developmental studies were performed in rats (dosed from day 16 of pregnancy until litter day 21 to 23). In all studies, intravenous (1, 9, and 90 mg/kg per day) instead of the inhalational route of drug administration was used. No malformations, maternal toxicity, or embryotoxicity were observed in pregnant rats or rabbits and their fetuses. Because of insufficient blood sampling timepoints in both rat and rabbit reproductive toxicity studies, AUC values were not available. However, in a subchronic study in rats at the 90-mg/kg per day IV dose, the AUC values were greater than 300 times the human exposure at the proposed clinical dose.

Zanamivir has been shown to cross the placenta in rats and rabbits. In these animals, fetal blood concentrations of zanamivir were significantly lower than zanamivir concentrations in the maternal blood.

There are no adequate and well-controlled studies of zanamivir in pregnant women. Zanamivir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Studies in rats have demonstrated that zanamivir is excreted in milk. However, nursing mothers should be instructed that it is not known whether zanamivir is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when RELENZA is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in pediatric patients below 12 years of age have not been established. In the three principal phase 3 treatment studies, 67 patients were 12 to 16 years of age. No definite differences in safety and efficacy were observed between these adolescent patients and young adults.

Geriatric Use: Of the total number of patients in 6 clinical treatment studies of RELENZA, 59 were 65 and over, while 24 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS: Adverse events that occurred with an incidence 1.5% in treatment studies are listed in Table 1. This table shows adverse events occurring in patients receiving RELENZA 10 mg inhaled twice daily, RELENZA in all inhalation regimens, and placebo inhaled twice daily (where placebo consisted of the same lactose vehicle used in RELENZA).

Table 1: Summary of Adverse Events 1.5% Incidence During Treatment

	RELENZA		
Adverse Event	10 mg b.i.d. Inhaled (n = 1132)	All Dosing Regimens* (n = 2289)	Placebo (Lactose Vehicle†) (n = 1520)

Body as a whole			
Headaches	2%	2%	3%
Digestive			
Diarrhea	3%	3%	4%
Nausea	3%	3%	3%
Vomiting	1%	1%	2%
Respiratory			
Nasal signs and symptoms	2%	3%	3%
Bronchitis	2%	2%	3%
Cough	2%	2%	3%
Sinusitis	3%	2%	2%
Ear, nose, & throat infections	2%	1%	2%
Nervous system			
Dizziness	2%	1%	<1%

*Includes studies where RELENZA was administered intranasally (6.4 mg 2 to 4 times per day in addition to inhaled preparation) and/or inhaled more frequently (q.i.d.) than the currently recommended dose.

†Because the placebo consisted of inhaled lactose powder which is also the vehicle for the active drug, some adverse events occurring at similar frequencies in different treatment groups could be related to lactose vehicle inhalation.

Additional adverse reactions occurring in less than 1.5% of patients receiving RELENZA included malaise, fatigue, fever, abdominal pain, myalgia, arthralgia, and urticaria.

The most frequent laboratory abnormalities in phase 3 treatment studies included elevations of liver enzymes and CPK, lymphopenia, and neutropenia. These were reported in similar proportions of zanamivir and lactose vehicle placebo recipients with acute influenza-like illness.

See PRECAUTIONS for safety information in patients with underlying respiratory disease.

OVERDOSAGE: There have been no reports of overdosage from administration of RELENZA. Doses of zanamivir up to 64 mg/day have been administered by nebulizer. Additionally, doses of up to 1200 mg/day for 5 days have been administered intravenously. Adverse effects were similar to those seen in clinical studies at the recommended dose.

DOSAGE AND ADMINISTRATION: RELENZA is for administration to the respiratory tract by oral inhalation only, using the DISKHALER device provided. **Patients should be instructed in the use of the delivery system. Instructions should include a demonstration whenever possible.**

The recommended dose of RELENZA for treatment of influenza in patients ≥12 years of age is 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart) for 5 days. Two doses should be taken on the first day of treatment whenever possible provided there is at least 2 hours between doses. On subsequent days, doses should be about 12 hours apart (e.g., morning and evening) at approximately the same time each day. There are no data on the effectiveness of treatment with RELENZA when initiated more than 2 days after the onset of signs or symptoms.

Patients scheduled to use an inhaled bronchodilator at the same time as RELENZA should use their bronchodilator before taking RELENZA. (See PRECAUTIONS regarding patients with chronic respiratory disease and other medical conditions.)

HOW SUPPLIED: RELENZA is supplied in a circular double-foil pack (a ROTADISK) containing 4 blisters of the drug. Five ROTADISKS are packaged in a white polypropylene tube. The tube is packaged in a carton with 1 blue and gray DISKHALER inhalation device (NDC 0173-0681-01).

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature). Keep out of reach of children. Do not puncture any RELENZA ROTADISK blister until taking a dose using the DISKHALER.

GlaxoWellcome
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

US Patent Nos. 4,627,432; 4,778,054; 4,811,731; 5,360,817; 5,648,379; 5,035,237; Des. 379,506

©Copyright 1999, Glaxo Wellcome Inc. All rights reserved.

Date of Issue RL no.